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TRIALS AND TRIBULATIONS IN DRUG DEVELOPMENT FOR NONALCOHOLIC STEATOHEPATITIS

Arun J. Sanyal, M.B.B.S., M.D. and **Naga Chalasani, M.D.**

[1]Div. of Gastroenterology, Hepatology and Nutrition, Dept. of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA 23298

[2]Div. of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN

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Nonalcoholic steatohepatitis (NASH) is a leading cause of chronic liver disease and is expected to surpass hepatitis C as the most common indication for a liver transplantation in the future [1]. There are currently no approved therapies for NASH. Together, these facts underscore the urgent need to develop effective strategies to contain the burden of disease due to NASH.

NASH is part of a spectrum of disease that is closely associated with obesity, insulin resistance and the metabolic syndrome in most subjects in the Western world [2]. It is estimated that almost 30% of the general population has excess hepatic fat while 2–4% may have NASH. The high prevalence of this condition makes the development of primary preventive strategies a public health priority. Unfortunately, studies aimed at the risk factors for NASH i.e. obesity have yielded mixed data and lifestyle modification is generally believed to improve insulin resistance and steatosis but is difficult to sustain for most individuals [3]. Thus there is an urgent need for safe and pharmacological treatments that reverse liver injury and fibrosis in individuals with NASH.

There is both good news and bad news regarding drug development for NASH. An extensive body of basic science literature has yielded a plethora of molecular targets to control steatosis, inflammation, cell death, and enhance repair mechanisms in affected individuals. The field is however still young and replete with poorly designed trials with a multitude of agents that provide little useful information. Drug development logic dictates the need to use

Correspondence: Arun J. Sanyal M.D., MCV Box 980341, Richmond, VA 23298-0341, asanyal@mcvh-vcu.edu, **Phone:** (804) 828 6314, **Fax:** (804) 828 2992, Naga Chalasani M.D., nchalasa@iupui.edu.

Conflicts of Interest:

Dr. Sanyal Serves as a consultant to Abbvie, Bristol Myers-Squibb, Genfit, Exhalenz, Islet Pharmaceuticals, Nimbus, Nitto-Denko and Tobira. His institution receives research funding from Gilead, Galectin, Novartis, Salix, Cumberland and Intercept Pharmaceuticals. He has also served as a non-remunerated consultant to Immuron and Echosens.

Dr. Chalasani: Serves as a consultant to Abbvie, Lilly, Boehringer-Ingelheim, Salix and Aegerion. His institution receives research funding from Gilead, Galectin, Cumberland and Intercept Pharmaceuticals.

agents whose mechanism of action relate to disease pathogenesis, demonstration of safety, choice of an optimal dose based on the therapeutic window, and a progression of clinical trials providing proof of concept and then proof of efficacy.

CGH has published in this issue and the October issue three well done early phase studies targeting three different pathways which advance these objectives.[4–6] These allow one to start identifying the agents likely to work and remove the rest from the menu of potential options. However, before getting rid of a given molecule as a therapy for NASH it is germane to review the potential reasons why the agent failed despite a well-constructed clinical trial.

There is a strong theoretical rationale for the use of all three agents studied. The first set of studies targeted phosphodiesterase 4 (PDE4) which modulates cyclic AMP (cAMP). cAMP dampens the inflammatory response and also potentially beneficial effects via modulation of AMP kinase activity a key regulator of metabolic homeostasis[7,8]. It is however theoretically possible that these beneficial effects could have been counteracted by activation of protein kinase A which could increase gluconeogenic drive. This was however not formally evaluated. Similarly, resveratrol and fatty acid bile acid conjugates (FABACs) have been shown to improve insulin sensitivity and decrease de novo lipogenesis respectively while promoting lipid mobilization from the liver[8-10]. The failure of two of the three agents to demonstrate benefit may also reflect the inadequacy of current preclinical models as surrogates for the human disease state and underscores the need for development of more relevant models and high throughput methods to screen molecules in the context of human disease for both efficacy and safety.

The studies with PDE4 inhibitors (ASP9831) moved logically from preclinical studies to a dose determination and a safety study to a proof of concept phase 2A study[5]. The studies were reasonably powered and the sponsors and investigators should be congratulated for their due diligence in evaluating this product. This study, while negative, informs about potential pitfalls in NASH related drug development. Many early phase trials focus on improvement in ALT. However, as clearly demonstrated in PIVENS and the TONIC trials, there is an early decrease in ALT regardless of treatment arm allocation in the first three months of entry in to the trial[11-13]. Thus, the failure to separate treatment from placebo could be a function of study duration to some degree rather than a true lack of effect. The study would have been bolstered if hepatic steatosis was also quantified in this study.

Indeed, the study with Aramchol used a change in hepatic steatosis as the primary endpoint and demonstrated a significant decrease in hepatic steatosis with high dose test drug (100 mg) compared to placebo[4]. As expected, ALT levels decreased in all three arms and were not significantly different, and it is unclear if this finding has any additional implications for future “go” or “no go” decisions for further development.

The third study of resveratrol took a proof of mechanism approach to demonstrate that high-dose resveratrol improved insulin resistance[6]. This is highly appropriate in early phase development and allows one to gain meaningful information with a small sample size. The methods were rigorous including the use of hyperinsulinemic euglycemic clamps for

quantification of insulin resistance and MR spectroscopy for analysis of hepatic steatosis. These careful studies demonstrated that pharmacological doses of resveratrol did not improve insulin sensitivity or hepatic steatosis in a 8 week period. It is however unclear if the 8 week study duration was long enough to change these pathophysiological parameters. Curiously, there was also no significant effect on several resveratrol target genes despite confirmation of compliance with pill counts and measurement of plasma levels of resveratrol. These findings indicate that it is likely that there are counter-regulatory factors that create a “resveratrol resistant” state in NASH. It is also noteworthy that unlike the other trials, use of active agent was associated with a significant early increase in ALT. This is worrisome although none of the subjects had clinically significant hepatotoxicity. It remains to be established whether this represents an adaptive response with induction of the enzyme.

In summary, three important early phase trials are presented targeting three unique mechanisms. While there are some questions about the reasons for failure of these agents, they demonstrate many best practices for therapeutic development for NASH and provide important lessons for future trials. There seems to be little reason to pursue resveratrol as a treatment for NASH and it is up to the sponsors of the PDE4 inhibitors to demonstrate improvement in hepatic steatosis or steatohepatitis. The potential application of Aramchol for NASH will require future trials based on efficacy endpoints.

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